AD_____

Award Number: DAMD17-02-1-0125

TITLE: Hot Flashes Among Prostate Cancer Patients Undergoing Androgen Deprivation Therapy: Psychosocial and Quality of Life Issues

PRINCIPAL INVESTIGATOR: James Coyne, Ph.D.

CONTRACTING ORGANIZATION: The University of Pennsylvania
Philadelphia, PA 19104-6205

REPORT DATE: December 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-12-2005	Annual	19 Dec 2004 – 19 Nov 2005

4. TITLE AND SUBTITLE
Hot Flashes Among Prostate Cancer Patients Undergoing Androgen Deprivation Therapy: Psychosocial and Quality of Life Issues

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-02-1-0125

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
James Coyne, Ph.D.

E-mail: jcoyne@mail.med.upenn.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The University of Pennsylvania
Philadelphia, PA 19104-6205

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Androgen deprivation therapy (ADT) is increasingly prescribed to patients with prostate cancer and brings with it an array of adverse effects. Hot flashes are a common side effect of ADT and are believed to be qualitatively similar to hot flashes among women receiving treatment for breast cancer. Currently no assessment protocols exist for objective assessments of hot flashes in prostate cancer patients, making it difficult to evaluate outcomes in clinical trials, educate clinicians and patients, or develop management and treatment strategies. This project will provide basic clinical epidemiological data concerning the nature, prevalence, and correlates of hot flashes among prostate patients receiving ADT, document the negative effects of hot flashes on sleep, fatigue, and quality of life, and compare the accuracy of alternative means of assessing hot flashes. The overarching goal is to not only understand the nature and importance of hot flashes, but to develop methodological standards for the assessment of hot flashes suitable to diverse applications. Results will have implications for the education of oncologists with respect to quality of life issues in prostate cancer, set standards for future research and clinical endeavors, and suggest directions for patient-oriented research to improve the wellbeing of prostate cancer patients.

15. SUBJECT TERMS
Prostate cancer, hot flashes, measurement, quality of life

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
U	U	U	UU	6	

Table of Contents

Introduction

Prostate cancer patients are often treated with androgen deprivation therapy (ADT) through chemical or surgical castration, a procedure resulting in the ablation of testosterone, an androgenergic hormone which is linked to increased proliferation of prostatic tumors. Hot flashes are a common side-effect of ADT, affecting up to 80% of prostate cancer patients treated with ADT. Although not medically threatening, hot flashes have been associated with sleep disruption, physical discomfort, and significant dimunation in quality of life. However, hot flashes are not directly observable phenomena and researchers must usually rely on self-reports of hot flashes, making it difficult to obtain accurate estimates of their frequency and intensity, particularly when hot flashes are nocturnal. Thus, hot flashes and their correlates are not well understood, and the most reliable and valid means of assessment remain unclear.

The current project examines hot flashes among prostate patients receiving ADT through the use of multi-method assessment combining self-report data with objective assessment of sternal conductence and actigraphy. This investigation will provide descriptive information on the nature, prevalence, and correlates of hot flashes; describe relationships of objectively assessed hot flashes to sleep patterns, fatigue, and quality of life; and compare assessment modalities in their ability to represent the occurrence of hot flashes. Approximately 150 patients will participate in a one-week assessment period at baseline and at six-month follow up. Assessment procedures include baseline self-report instruments designed to assess demographic variables, retrospecive reports of the frequency and intensity of hot flashes, fatigue, activity level, quality of life, nocturia, psychological distress, and coping. In addition, during each seven-day assessment period, participants will complete daily symptom diaries designed to assess the frequency, intensity, and duration of hot flashes, and the life and role interference associated with hot flashes. During this seven-day period, participants will be fitted with a small, wristwatch-sized accelerametor designed to record activiy-levels during wakefulness and sleep. During two 24-hour periods at the beginning and end of each seven-day assessment period, participants will wear a sternal skin conductance monitor designed to objectively assess the occurance of hot flashes. These sources of data (self-report, actigraphy, and sternal skin conductance) will be combined to allow for a clearer picture of the frequency, intensity, and duration of hot flashes, and, ultimately, will allow for a better assessment of how these influence quality of life and functional status.

Body

This project received full human subjects approval by the Department of Defense Grants Officer on March 12, 2003. Since that time, a Postdoctoral Research Fellow has served as the position of project manager and meetings with medical personnel and the investigator team were conducted to finalize research procedures. The investigative team convenes on a biweekly basis to review the progress of the study and address any challenges to completing the study's goals.

Research assistants were hired in early 2004 and trained to recruit subjects and collect data during home visits. Janet Carpenter, Ph.D., RN, a grant consultant, who is an expert in the assessment of hot flashes in cancer patients has provided three training sessions to study staff on the subjective assessment of hot flashes, the use of sternal conductance monitoring and associated software, and on associated data analyses. Her last site visit was in March 2005. Recruitment of patients began in May 2004, and the first baseline assessment occurred in June 2004. To date, 54 men have completed the baseline assessment, and 4 men are currently being run. Also, 24 men have completed a 6-mo assessment. We have tripled the number of baseline assessments since the annual 2004 report making this the largest data set concerning objective assessment of hot flashes in men with prostate cancer that has ever been assembled.

In line with our study's goal of testing the feasibility of sternal skin conductance in men, early assessments revealed some distinct limitations with this mode of hot flash measurement. It should be noted that the view of sternal skin conductance as the "gold standard" for objective

assessment of hot flashes has been based entirely on studies of menopausal women and women with breast cancer, and ours is the first study to extend this approach to men.

The equipment used in sternal conductance has demonstrated some short comings when worn by patients in their everyday environments, and we have been working with the supplier, Biolog corporation, to overcome these difficulties. As well, the presence of chest hair has proven to be an obstacle to ease of use. Removal of chest hair is not an option, as this also removes skin which, in turn, negatively impacts skin conductance. To overcome this, we have conducted literature reviews to find other comparable locations to measure skin conductance that would meet the requirements of sweat gland density and low psycho-activity of sweat glands, and are piloting these alternative sites. As well, we have found that measurement artifacts are common. We have identified that placing pressure on the electrode, which participants are likely to do in response to itchiness, as well as exercise and cell phone use creates artifact. We have also created surveys to obtain the reasons why participants refuse to wear the Biolog monitor as well as a survey on the experience of wearing a monitor. Overall, we have taken an active, problem-solving approach to tackling problems that are inherent in the assessment of sternal conductance in active, ambulatory persons, but also that are specific to men.

In terms of sociodemographic information, the sample thus far is a primarily older (M = 70.42 yrs, R = 53 to 88yrs), married (78%) and Caucasian (74%), although another 22% self-identify as African-American. All but 2 participants had at least a high school education and 34% had completed graduate or professional school. About one-quarter (28%) of the sample was working full-time, although most (62%) were retired. All but 1 participant had health insurance and 38% received annual income over $70,000.

The Hot Flash Questionnaire, which is completed prior to the first 24-hr objective hot flash monitoring session, revealed that 80% of the participants experienced hot flashes. Of those who had hot flashes, the daily hot flash average was 5.4 (SD = 3.9) in the past week and 32% and 30% reported their hot flashes were bothersome *a little* and *some*, respectively. For the baseline assessment, 70% of the men agreed to wear the hot flash monitor and event mark when they experienced a hot flash. See table 1 for the average number of hot flashes for the two 24-hr periods during the baseline assessment.

Table 1

The occurrence of hot flashes among prostate cancer patients receiving androgen deprivation therapy

	M (SD)
1st 24-hr Objective Hot Flashes	7.4 (9.2)
2nd 24-hr Objective Hot Flashes	7.2 (8.9)
1st 24-hr Subjective Hot Flashes	7.3 (5.3)
2nd 24-hr Subjective Hot Flashes	6.5 (5.3)

Our contention that subjective reports of hot flashes are inadequate to understand the phenomena has been supported by the current data. Of the 461objective hot flashes, 227 (49%) were accompanied by an event mark, indicating a 51% false-negative rate. Conversely, of the 426 event marks, 227 (53%) were validated by increases of skin conductance, indicating a 47% false-positive rate. Thus, men are underreporting the occurrence of hot flashes about 50% of the time and misinterpret somatic or psychosomatic experiences as hot flashes almost 50% of the time.

We also examined the occurrence of hot flashes during sleep and wake times throughout a 24-hr period. Sleep and wake times were determined by the Actiware software by comparing

epochs of activity levels. We found that the mean number of objectively reported hot flashes during wake times is significantly higher ($t(34) = 5.29$, $p = <.001$) relative to hot flashes during sleep. This indicates that during most hot flashes men are relatively active, which is likely to interrupt their sleep at night.

Sleeping through hot flashes is a reasonable explanation for the occurrence of false-negative hot flashes. Of the 225 false-negative hot flashes, 155 (69%) occurred while the men are awake, which is significantly higher than false negatives while sleeping ($t(34) = 5.49$, $p = <.001$). Therefore, men are not detecting most hot flashes for reasons other than sleep.

These preliminary data suggest that individuals vary greatly in their ability to accurately identify hot flashes, supporting our aim of developing more accurate objective indices of this phenomenon. In the upcoming year, we will finish recruiting participants and begin data analyses for manuscripts, conference presentations, and the final report. One focus of our analysis will be to provide estimates of the effects of reliance on subjective self-reports as outcome measures in existing clinical trials. We will model the effects on effect sizes. Importantly, we will establish parameters, including a formal power analysis of a study planned for subsequent to this project examining acupuncture in terms of effects on subjective versus objective measures of hot flashes. Aside from allowing evaluation of the mechanism by which acupuncture might affect complaints of hot flashes, this study will provide a model for future research, which based on the results of present study, must now distinguish between objective versus subjective effects of treatment. It is likely that treatments differ in the extent to which they simply affect patient perceptions or self-report versus the occurrence of the objective event of a hot flash.

Key Research Accomplishments

- Research staff have been hired and trained.
- Initial referral sources have been expanded, active recruitment of patients continues.
- Databases have been created and preliminary analyses are ongoing as data are entered and cleaned.

Reportable Outcomes

At this point, no manuscripts, abstracts, presentations; patents and licenses; development of cell lines, tissue or serum repositories; infomatics; funding; employment or research opportunities have been published, applied for, or obtained based on experience with or outcomes of this study.

A review on hot flashes and endogenous opioids has been accepted by *The Lancet* for publication as a comment article. This article credits the DOD for partial support of its preparation. The publication date has not been announced. Also, a poster presentation will submitted for the annual 2006 Society of Behavioral Medicine conference held in April. The topic will be Anxiety and Hot Flashes in Prostate Cancer Patients Receiving Androgen Deprivation Therapy. We will conduct analyses for the poster in the next month.

Conclusions

Since receiving final approval in Year 2, we have finalized procedures, hired and trained staff, and are currently actively enrolling patients. A no-cost extension request has been submitted and granted in order to meet our accrual goals and fulfill our obligations.

References

None

Appendices

None